Notice of Allowability	Application No.	Applicant(s)	
	10/718,856	MARIELLA ET AL.	
	Examiner	Art Unit	
	Stephanie K. Mummert	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *12/7/06*.

2. ☒ The allowed claim(s) is/are *1,17,18,21,38-40,42,59 and 60*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *030806* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

JEFFREY FREDMAN
PRIMARY EXAMINER
3/15/a

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Eddie Scott on March 10, 2006 and March 14, 2006.The application has been amended as follows:

1. A method of constructing poly-nucleotides, comprising the steps of:

a) providing a mixture comprising a nucleic acid template chemically coupled to a protein ligase and single stranded DNAs complementary to the template, for ligation,

b) ligating strands of DNA using a protein ligase and a complementary sequence as a template, wherein said step of ligating utilizes hybridization to a complementary template which has been chemically coupled to a protein ligase enzyme.

17. The method of constructing polynucleotides of claim 1 including repeatedly adding single-stranded DNA to a growing piece of double-stranded DNA which is tethered to a protein ligase enzyme.

18. The method of constructing polynucleotides of claim 1 including repeatedly adding double-stranded DNA to a growing piece of double-stranded DNA which is tethered to a protein ligase enzyme.

21. A method of constructing very long, double-stranded synthetic poly-nucleotides comprising the steps of:

a) providing a mixture comprising a nucleic acid template chemically coupled to a protein ligase and single stranded DNAs complementary to the template, for ligation,

b) providing a multiplicity of oligonucleotides,

c) sequentially hybridizing said oligonucleotides to each other, and

d) enzymatic ligating said oligonucleotides to provide a contiguous piece of DNA of predetermined sequence, wherein said step of enzymatic ligating utilizes hybridization to a complementary template which has been chemically coupled to a protein ligase enzyme.

38. The method of constructing polynucleotides of claim 21 including repeatedly adding single-stranded DNA to a growing piece of double-stranded DNA which is tethered to a protein ligase enzyme.

39. The method of constructing polynucleotides of claim 21 including repeatedly adding double-stranded DNA to a growing piece of double-stranded DNA which is tethered to a protein ligase enzyme.

40. The method of constructing polynucleotides of claim 1 including repeatedly adding either single-stranded DNA or double-stranded DNA to a growing piece of double-stranded DNA which is tethered to a protein ligase enzyme.

42. A method of constructing very long, double-stranded synthetic polynucleotides comprising the steps of:

a) providing a mixture comprising a nucleic acid template chemically coupled to a protein ligase and single stranded DNAs complementary to the template, for ligation,

b) providing a multiplicity of short single-stranded oligonucleotides,

c) sequentially hybridizing said short single stranded oligonucleotides to each other, and

d) enzymatic ligating said short single-stranded oligonucleotides to provide a contiguous piece of double stranded DNA of predetermined sequence, wherein said step of ligating utilizes hybridization to a complementary template which has been chemically coupled to a protein ligase enzyme.

59. The method of constructing polynucleotides of claim 42 including repeatedly adding single-stranded DNA to a growing piece of double-stranded DNA which is tethered to a protein ligase enzyme.

60. The method of constructing polynucleotides of claim 42 including repeatedly adding double-stranded DNA to a growing piece of double-stranded DNA which is tethered to a protein ligase enzyme.

Reasons for Allowance

1. The following is an examiner's statement of reasons for allowance:

There is no teaching in the prior art wherein strands of DNA are ligated utilizing a complementary template chemically coupled to a ligase enzyme. The closest prior art, Virtanen et al. (US PgPub 2005/0076805; June 2002) teaches a detection system for measuring the presence of an analyte in a sample, and includes a ligase enzyme linked to a DNA segment (see Figures 7 and 8A-B). While Virtanen discloses a ligase attached to a DNA segment, the attached DNA segment does not function the same way as the chemically coupled DNA in the instant application because the attached DNA acts as a guide to control the physical location of the

ligase and does not participate in the ligation reaction. The chemically coupled DNA in the instant application participates in the ligation reaction and serves as a template strand for the hybridization and ligation of complementary single strands of DNA. It is noted that because the ligase is chemically coupled to the DNA segment distinguishes over situations where the ligase is momentarily tethered to the DNA during the ligation process.

The word 'protein' was inserted prior to the term ligase to distinguish over the tethered RNA ribozyme ligase disclosed by Lizardi et al. (US Patent 5,652,107; July 1997). While Lizardi teaches the ligation of probes bound to a complementary target, using a ligase tethered to a 'holdfast' sequence, the method does not require that the ligase be attached to the probes which are being ligated. For example, in Figure 1, the ribozyme ligase **8** ligates two probes (**19, 20**) hybridized adjacent to one another and not connected to the ribozyme ligase. Furthermore, while the reference discloses an improvement in ligation efficiency due to the ribozyme being held in proximity to its point of operation (col. 2, lines 58-60), Lizardi specifically teaches away from using the ribozyme ligase with DNA targets. Lizardi states that "because RNA targets suitable for detection are in most cases much more abundant in samples than their corresponding DNA targets" and that "it is an objective of this invention to overcome the limitation of existing binary probe assays that use DNA binary probes" (col. 1 line 63 to col. 2, line 15). While Virtanen and Lizardi both disclose methods which incorporate ligases which are tethered to a nucleotide sequence, they do not meet the limitation of the claims as written and there would be no motivation to combine these references with prior art references within the art of gene synthesis using ligation. Therefore, the claimed invention is novel and non-obvious over the prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie K. Mummert whose telephone number is 571-272-8503. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephanie K Mummert
Examiner
Art Unit 1637

SKM

JEFFREY FREDMAN
PRIMARY EXAMINER
3/15/06